UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JORJ TERRY ULRICH
and ALAN WORLAND WHEELER

Appeal No. 2005-0107
Application No. 09/402,273

HEARD February 8, 2005

Before WILLIAM F. SMITH, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 2, 6-8, and 15-23, all of the claims remaining. Claims 1 and 18 are representative and read as follows:

1. A pharmaceutical composition capable of selectively enhancing a TH_1 response over a TH_2 response, comprising tyrosine, an allergen or allergen extract, and 3-DMPL.

18. A composition according to claim 1, wherein the allergen or the allergen extract is not modified by reaction with a cross-linking agent.

The examiner relies on the following references:

Prieels et al. (Prieels)	5,750,110	May 12, 1998
Frank et al. (Frank)	5,795,862	Aug. 18, 1998
van Wijnendale et al. (van Wijnendale)	WO 92/16556	Oct. 1, 1992
Wheeler et al. (Wheeler)	WO 96/34626	Nov. 7, 1996

Marsh, "Preparation and Properties of 'Allergoids' Derived from Native Pollen Allergens by Mild Formalin Treatment," Int. Arch. Allergy, Vol. 41, pp. 199-215 (1971)

Holen et al. (Holen), "Specific T cell lines for ovalbumin, ovomucoid, lysozyme and two OA synthetic epitopes, generated from egg allergic patients' PBMC," Clin. Exp. Allergy, Vol. 26, pp. 1080-1088 (1996)

Hoyne et al. (Hoyne), "Peptide-mediated regulation of the allergic immune response," Immunology and Cell Biology, Vol. 74, pp. 180-186 (1996)

Claims 1, 2, 6-8, 15-17, and 19-23 stand rejected under 35 U.S.C. § 103 as obvious in view of Wheeler, van Wijnendale, and Frank.

Claim 18 stands rejected under 35 U.S.C. § 103 as obvious in view of Wheeler, van Wijnendale, Frank, Marsh, Pieels, and Hoyne.

Claims 1 and 23 stand rejected under 35 U.S.C. § 103 as obvious in view of Wheeler, Holen, van Wijnendale, Pieels, and Hoyne.

We affirm.

Background

The specification discloses "formulations for use in desensitisation therapy of allergy sufferers." Page 1. "Two subclasses of T cells, TH1-like and TH2-like[,] interact with one another via various messenger molecules. In an allergic subject it appears that there is a greater allergen specific TH2 than a TH1 activity. . . . A change in the above situation to one where there is greater allergen specific TH1 rather than TH2

activity is thought to be an important component of immunotherapy leading to a clinical benefit." Id.

The formulations disclosed by the specification to be useful in desensitization therapy comprise three components: an allergen, tyrosine, and 3-DMPL.

> 3 De-O-acylated monophosphoryl lipid A (hereinafter 3-DMPL or "MPL") is known from GB-A-2 220 211, corresponding to U.S. Patent No. 4,912,094. . . . Chemically it is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem Montana. A preferred form of 3 De-O-acylated monophosphoryl lipid A is disclosed in International Publication No. 92/16556.

Page 1 (as amended in the preliminary amendment filed October 1, 1999). The specification discloses that "3-DMPL is an example of a substance that can enhance the TH1 over TH2 directing properties of administered allergens." Id.

The specification provides a working example showing the effect that various compositions had on immunoglobulin levels when administered to mice. "[T]he combination of allergen + tyrosine + MPL induces less allergen specific IgE antibody than the other combinations [allergen alone, allergen + tyrosine, and allergen + MPL]. Furthermore, the ratio of IgG2a or IgG2b to IgG1 antibodies is greater . . . in the mice given allergen+tyrosine+MPL than in any other group of mice. This is indicative of a better ratio of TH1 cell induction over TH2 cell induction in this group." Page 6.

Discussion

1. Claims 1, 2, 6-8, 15-17, and 19-23

The claims stand or fall together. Appeal Brief, page 8. We will consider claim 1 as representative; claims 2, 6-8, 15-17, and 19-23 will stand or fall with claim 1. Claim 1

is directed to a pharmaceutical composition "capable of selectively enhancing a TH_1 response over a TH_2 response," comprising tyrosine, an allergen, and 3-DMPL.

The examiner rejected claims 1, 2, 6-8, 15-17, and 19-23 as obvious in view of Wheeler, van Wijnendale, and Frank. The examiner correctly characterized Wheeler as disclosing a composition for "desensitization therapy of allergy sufferers," comprising tyrosine and an allergen, but not 3-DMPL. Examiner's Answer, page 4. The examiner cited van Wijnendale as "teach[ing] 3D-MPL is a known adjuvant used in vaccine . . . for stimulating antigen specific neutralizing antibody and cell mediated immunity (Delayed type hypersensitivity, DTH), which is a TH1 immune response." Id. Finally, the examiner cited Frank for its disclosure of a composition comprising a flea allergen and "the Ribi adjuvant from Ribi ImmunoChem [which] enhances the immune response of any antigen." Id.

The examiner concluded that "it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant . . . in a pharmaceutical composition comprising tyrosine and modified allergen for desensitization therapy as taught by [Wheeler]." Id. The examiner found motivation to combine the references in van Wijnendale's "teach[ing] that the adjuvant formulations containing 3D-MPL are able to induce specific T cell responses such as effector cell mediated (DTH) immune response where DTH is a TH1 response (See page 29, lines 8-16 . . .)," as well as in Frank's teaching that combining an allergen with an adjuvant such as "Ribi adjuvant" results in enhanced host immune response. Examiner's Answer, page 5.

We agree with the examiner that the cited references support a prima facie case of obviousness. To paraphrase the examiner's reasoning, Wheeler teaches a composition for desensitization therapy comprising tyrosine and an allergen; Frank teaches that adjuvants, including "Ribi adjuvants", are "substances that generally enhance the immune response of an animal to a specific antigen" (column 42); and van Wijnendale teaches that "known adjuvants . . . include . . . 3D-MPL (3Deacylated monophosphoryl lipid A)." Page 7. Therefore, it would have been obvious to those of skill in the art to add the 3-DMPL adjuvant taught by van Wijnendale to the composition taught by Wheeler, with the expectation that the known adjuvant would provide the expected effect of enhancing the immune response to an allergen.

Appellants argue that Wheeler is not available as prior art because a declaration they submitted under 37 CFR § 1.131 shows that they completed their invention prior to Wheeler's publication date. See the Appeal Brief, pages 19-20.

This argument is not persuasive. The effective filing date of the instant application is April 3, 1998 (the date Appellants filed their PCT application), while Wheeler was published on November 7, 1996. Although Appellants claim priority under 35 U.S.C. § 119 to a British application filed April 5, 1997, § 119 provides that "no patent shall be granted on any application for patent for an invention which had been . . . described in a printed publication in any country more than one year before the date of the actual filing of the application in this country." See also Kawai v. Metlesics, 480 F.2d 880, 885, 178 USPQ 158, 162-63 (CCPA 1973) ("[T]he 'right of priority' accorded by section 119 can aptly be described as a right to prove a date of invention no earlier than the date of the foreign filing." (emphasis removed)).

Appellants also argue that Wheeler is not prior art because "SmithKline Beecham PLC owned both the WO 96/34626 reference [Wheeler] and the subject matter of the instant application at the time the claimed invention was made (35 U.S.C. § 103(c))." Appeal Brief, pages 20-21. However, § 103(c) only applies to "[s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), or (g) of section 102." Here, Wheeler qualifies a prior art under § 102(b), so § 103(c) does not apply.

Appellants also argue that, even if Wheeler is available as prior art, the references cited by the examiner do not support a prima facie case of obviousness. Appellants point out that claim 1 is directed to a composition "capable of selectively enhancing a TH_1 response over a TH_2 response," and argue that the examiner has not adequately shown that the cited references meet this limitation. Appellants argue that the evidence does not support either the examiner's position that the DTH (delayed type hypersensitivity) response discussed by van Wijnendale is a TH_1 response or the examiner's position that enhancement of a TH_1 response over a TH_2 response is an inherent property of 3-DMPL. Reply Brief, pages 12-13.

Appellants cite references which, they assert, contradict both of the positions taken by the examiner. Although the references were submitted together with the Reply Brief, the examiner apparently did not refuse to enter them.[1] The examiner simply noted that the "Reply Brief filed 7/8/04 has been entered and considered but no response by the examiner is deemed necessary." See the communication mailed July

[1] Cf. (then-applicable) 37 CFR § 1.195 ("Affidavits, declarations, or exhibits submitted after the case has been appealed will not be admitted without a showing of good and sufficient reasons why they were not earlier presented.").

22, 2004. Appellants cite Akahira-Azuma[2] as evidence that "both Th_1 and Th_2 may be implicated in early delayed type hypersensitivity" and cite both Johansen[3] and Yang[4] as evidence that "MPL has different T cell responses when exposed to different antigens." See the Reply Brief, pages 12-13.

We have considered Appellants' argument in light of the evidence of record, but do not find it persuasive. The references submitted with the Reply Brief do provide some evidence that both TH_1 and TH_2 may contribute to some aspects of delayed-type hypersensitivity (Akahira-Azuma) and that, in some contexts, 3-DMPL can induce a mixed TH_1/TH_2 response (Johansen and Yang). However, when determining obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill." In re Hedges, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986). In addition, "[o]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Here, the evidence shows that – as of the instant application's effective filing date – those skilled in the art recognized 3-DMPL as an adjuvant known to enhance a TH_1 response over a TH_2 response. The instant specification, in a section with the heading "Background of the Invention," states that "3-DMPL is an example of a

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[2] Akahira-Azuma et al., "Early delayed-type hypersensitivity eosinophil infiltrates depend on T helper 2 cytokines and interferon-γ via CXCR3 chemokines," Immunology, Vol. 111, pp. 306-317 (2004).
[3] Johansen et al., "Immunogenicity and protective efficacy of a formalin-inactivated rotavirus vaccine combined with lipid adjuvants," Vaccine, Vol. 21, pp. 368-375 (2003).
[4] Yang et al., "Mechanisms of monophosphoryl lipid A augmentation of host responses to recombinant HagB from Porphyromonas gingivalis," Infection and Immunity, Vol. 70, pp. 3557-3565 (2002).

substance that can enhance the TH1 over TH2 directing properties of administered allergens." Page 1, lines 30-31.[5] Ulrich,[6] confirms that, as stated in the specification, 3-DMPL was known to enhance the TH_1 response to an antigen. Ulrich states that "[t]he hallmarks of Th1-type help are antigen-specific DTH and the predominance of an IgG2a immunoglobulin isotype, particularly following secondary responses. The role of MPL® in promoting these markers of Th1 response has been documented previously."[7]

Thus, even though the references cited by the examiner do not disclose that 3-DMPL selectively enhances a TH_1 response over a TH_2 response, it is apparent that this property of 3-DMPL was known to those skilled in the art. Therefore, those skilled in the art would have reasonably expected the addition of 3-DMPL to Wheeler's tyrosine- and allergen-containing composition to result in enhancement of a TH_1 response over a TH_2 response.

Appellants also argue that van Wijnendale is nonanalogous art, because it addresses the treatment of HIV/AIDS, not treatment of allergies. Reply Brief, page 13.

This argument is also not persuasive. "Two criteria have evolved for determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the reference is not within the field of

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[5] See also the amendment filed October 1, 1999, which added the headings "Background of the Invention" at page 1, between lines 4 and 5, and "Summary of the Invention" at page 1, between lines 31 and 32.

[6] Ulrich et al., "Monophosphoryl lipid A as an adjuvant. Past experiences and new directions," Pharm. Biotechnol., Vol. 6, pp. 495-524 (1995), copy attached. Ulrich is cited in the Johansen reference attached to Appellants' Reply Brief. Although the examiner did not rely on Ulrich, our citation of it does not constitute a new ground of rejection. Cf. Hedges, 783 F.2d at 1039, 228 USPQ at 686 ("Hedges relied on these references . . . for his argument that viewed as a whole the body of prior art teaches away [from the claimed invention]. The Solicitor should not be constrained from pointing to other portions of these same references in contravention of Hedges' position.").

[7] Ullrich uses "MPL®" as a synonym for 3-DMPL. See page 498 (MPL® is "3-O-Deacylated monophosphoryl lipid A" that has been further purified by chromatography).

the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved." In re Clay, 966 F.2d 656, 658, 23 USPQ2d 1058, 1060 (Fed. Cir. 1992).

In this case, the prior art reference relates to immunotherapy for treatment of disease (HIV infection), while the claimed composition relates to immunotherapy for treatment of allergies. In both cases, the therapies are directed toward provoking an immune response against a particular antigen. We therefore conclude that van Wijnendale would have been considered "reasonably pertinent to the particular problem with which the inventor is involved," and therefore analogous. In addition, Frank shows that adjuvants (like those used by van Wijnendale) were also used in the field of desensitization therapy for allergies, further confirming the analogous nature of the references.

Appellants also argue that Wheeler's tyrosine/allergen composition can be combined with van Wijnendale's 3-DMPL only with the benefit of hindsight. Reply Brief, page 14. Finally, Appellants argue that Frank does not disclose that the so-called "Ribi adjuvants" are 3-DMPL. Id., pages 14-15.

These arguments are not persuasive. Motivation to combine an adjuvant with Wheeler's tyrosine- and allergen-containing composition is provided by Frank and van Wijnendale. Frank teaches that "[a]djuvants are typically substances that generally enhance the immune response of an animal to a specific antigen," and that "[s]uitable antigens include . . . aluminum-based salts; . . . Ribi adjuvants (available from Ribi ImmunoChem Research, Inc., Hamilton, Mont.); and saponins and their derivatives, such as Quil A." Column 42, lines 23-34).

Van Wijnendale, in turn, teaches that "various known adjuvants . . . include, but are not limited to, aluminium [sic] hydroxide, muramyl dipeptide and saponins such as Quil A, 3D-MPL (3Deacylated monophosphoryl lipid A) or TDM." Page 7, lines 8-11. See also page 8, lines 31-35 (preferred aspect of the invention includes 3D-MPL as adjuvant). Thus, the cited references, considered as a whole, taught that adding an adjuvant enhances the immune response to a specific antigen; that 3-DMPL was among the known adjuvants commonly used to achieve this end; and that 3-DMPL was preferred among the "various known adjuvants" discussed by van Wijnendale. These teachings, in combination, would have motivated a person of ordinary skill in the art to add van Wijnendale's 3-DMPL to Wheeler's composition.

For the reasons discussed above, we agree with the examiner that the cited references support a prima facie case of obviousness, which has not been rebutted. The rejection of claim 1 under 35 U.S.C. § 103 is therefore affirmed. Claims 2, 6-8, 15-17, and 19-23 fall with claim 1.

2. Claim 18

The examiner rejected claim 18 as obvious in view of Wheeler, van Wijnendale, Frank, Marsh, Pieels, and Hoyne. Claim 18 is directed to the composition defined by claim 1, with the added limitation that the allergen is "not modified by reaction with a cross-linking agent." Of the additional references cited in support of this rejection, the examiner relies only on Marsh for the additional limitation found in claim 18.[8]

[8] It is unclear to us why the examiner felt that Pieels and Hoyne were necessary to support a rejection of claim 18, but not claim 1, when nothing in those references was cited with respect to the "unmodified allergen" limitation of claim 18.

The examiner states that Marsh "teach[es] unmodified native allergen such as pollen allergen and chemically modified such as formalinized allergen." Examiner's Answer, page 6. The examiner concluded that

> it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the 3-DMPL adjuvant as taught by [Pieels] or [van Wijnendale] in a pharmaceutical composition comprising tyrosine, modified or unmodified allergen or allergen extract(s) as taught by [Wheeler] as taught by [Frank] or Marsh et al. for a pharmaceutical composition that would have selectively enhanced a TH1 response over a TH2 response as taught by Hoyne et al. and [Pieels]

Examiner's Answer, pages 6-7 (emphasis added).

We agree with the examiner that the composition of claim 18 would have been obvious to those of ordinary skill in the art. Marsh teaches that native antigens are of limited use in desensitization therapy because the necessary antigen doses are often difficult to achieve and desensitization therapy "usually accomplishes only partial relief at high expenditure, with the risk of general allergic reactions along the way." Page 199. Marsh discloses modification of native allergens with formaldehyde, with the formation of methylene bridges between amino acid residues and additives, but only a "small degree of inter-protein cross-linkage." Page 201. Marsh reports that formaldehyde modification "eliminate[d] over 99% of the skin and leukocyte cell reactivity in allergic man, while largely retaining the original immunizing properties of the native molecules with respect to 'blocking antibody' production in animals and man." Page 212.

Thus, we agree with the examiner that it would have been obvious to a person of ordinary skill in the art to modify Wheeler's tyrosine- and allergen-containing composition to substitute the formaldehyde-modified allergen disclosed by Marsh for the

glutaraldehyde-crosslinked allergen used by Wheeler. Motivation to do so is provided by Marsh, which discloses that "much higher usefully immunizing levels of allergoid [i.e., formaldehyde-modified allergens] could be administered to allergic individuals than is presently possible with native allergen." Sentence bridging pages 212-213. As discussed above, those skilled in the art would have also found it obvious to include 3-DMPL in the composition in order to enhance the immune response to the specific antigen.

Appellants argue that "[b]ecause claim 1 is not rendered obvious by the combination of [Wheeler] in view of [van Wijnendale] and [Frank] as set forth above, it follows that claim 18 cannot be rendered obvious by the cited combination of references. . . . The examiner cites Marsh for the teaching of an unmodified allergen and a chemically modified allergen such as formalinized allergen. As already noted, this teaching will not serve to obviate the patentability of claim 18 due to its dependency on claim 1." Reply Brief, page 16.

We have concluded that claim 1 is rendered obvious by the combination of Wheeler, van Wijnendale, and Frank. Appellants' argument – that claim 18 is not obvious because claim 1 is not obvious – therefore does not persuade us that the examiner's rejection of claim 18 is in error. The rejection of claim 18 is affirmed.

Summary

The cited references support a prima facie case of obviousness which has not been rebutted or overcome. The rejections under 35 U.S.C. § 103 are affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

William F. Smith)
Administrative Patent Judge)
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